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Brachytherapy 12 (2013) 560−566

BRACHYTHERAPY

Definitive high-dose-rate endobronchial brachytherapy of bronchial stump for lung cancer after surgery

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ABSTRACT

PURPOSE: The aim of this work was to evaluate outcomes after definitive high-dose-rate endobronchial brachytherapy (HDR-BT) for lung cancer.

METHODS AND MATERIAL: We treated 34 patients after surgery for lung cancer, without nodal or distant metastases, with HDR-BT. Two groups were analyzed, one with local recurrence in stump after prior surgery ($n = 13$) and a second with nonradical primary lobar resection found in histopathologically positive margins ($n = 21$). There were 27 men and 7 women with a median age of 57.4 years. Twenty-five patients received sole brachytherapy with 4 fractions of 7.5 Gy and 9 received combined treatment consisting of 2 fractions of 6 Gy (HDR-BT) and 50 Gy from external beam radiotherapy. Overall survival time (OS) and overall disease-free survival time (OFS) were compared with prognostic factors.

RESULTS: The complete local and radiologic response rate evaluated at the first month after HDR-BT was 73.5% (25/34). The partial response rate was 26.5%. OFS time in total group was 17.4 months; OS was 18.8 months. Differences were found in OS between both groups—primary tumor or recurrence (log-rank test, $p = 0.048$). Differences were not found according to gender ($p = 0.36$), clinical stage ($p = 0.76$), histopathology ($p = 0.93$), treatment dose ($p = 0.45$), sole or combined treatment ($p = 0.16$), or grade of remission in week 4 ($p = 0.15$).

CONCLUSIONS: HDR-BT of a stump recurrence or after nonradical resection leads to a long-term OS rate in patients with localized lung cancer and could be considered curative. We found no correlations between OS and chosen clinical data; adjuvant HDR-BT gave better results.

Keywords: Definitive brachytherapy; Radical brachytherapy; Lung cancer; Recurrence; Stump

Lung cancer is the leading cause of cancer death with 5-year survival rates reaching only 10−12% over the last 20 years (1). The lung cancer failure rate remains unacceptably high, despite major advances over the past 40 years in the fields of surgery, radiotherapy and chemotherapy. In general, upon diagnosis 25−30% of the non−small-cell lung cancer patients present with tumors confined to the lung (stage I or II) and only 40−50% of them can be resected for cure; 30% have locally advanced disease (stage III) and the remaining 40−45% have distant metastases (stage IV) (1). Even with resectionable tumors, we often observe local failures infiltrating a stump; additionally, after radical surgery some pathologic samples show the presence of cancer cells. Treatment choice in these cases is not well-established. High-dose-rate endobronchial brachytherapy (HDR-BT) of lung cancer is a well-established method for the local treatment of patients with tumors of the tracheobronchial system (2−4). HDR-BT plays a limited but specific role in definitive treatment with curative intent in selected cases of early endobronchial disease (T1−2) as well as in the postoperative treatment of small residual peribronchial disease (5−7). Other indications include intraluminal HDR-BT of the bronchial stump

Received 4 February 2013; received in revised form 4 May 2013; accepted 7 May 2013.

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1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2013.05.002

after resection with positive resection margins combined with postoperative external beam radiotherapy (EBRT) and HDR-BT with curative intent considered as a boost for minor residual disease within a combined nonsurgical radical approach. This may apply to small cell lung cancer after remission induced by chemotherapy and EBRT or for non–small-cell lung cancer as a boost after remission induction by EBRT (with or without chemotherapy) (3, 4, 6–13). However, HDR-BT as a curative treatment has not been extensively studied, especially in stump recurrences or stump infiltrations.

The aim of this work was to evaluate outcomes after definitive HDR-BT for lung cancer. We analyzed results of HDR-BT of local recurrences in stump after surgery or as adjuvant therapy after nonradical surgery.

Methods and material

Material

Between January 2003 and December 2007, 34 patients after surgery for lung cancer without nodal or distant metastases qualified for curative HDR-BT. We distinguished two groups with different indications. In the first group, we analyzed cases with local recurrence in bronchus stump (only) after surgery ($n = 13$), and in the second group, cases with nonradical primary lobar resection found in histopathologically positive margins ($n = 21$). There were 27 men and 7 women with a median age of 57.4 years. Median time to recurrence after surgery was 11.2 months. In all cases, patients underwent lobar resection. Patients were not irradiated before. Brachytherapy was the treatment of choice owing to good localization of tumor (stump) during the bronchofiberoscopy and low local advancement. In 9 cases, HDR-BT was combined with EBRT owing to more advanced primary cancer. This decision was made individually.

All patients have gone through prior bronchofiberoscopy and x-ray/CT for histologic diagnosis and for evaluation of tumor extent. Most of patients were in good performance status (according to the Eastern Cooperative Oncology Group-Zubrod-World Health Organization score): 12 (35.3%) had a score of 1 and 22 (64.7%) had a score of 2. Patient characteristics are summarized in Table 1.

Table 1
Clinical characteristics of patients

Clinical data	*n* (%)
Total	34
Men	27 (79.4)
Women	7 (20.6)
Age, median (range)	57.4 (47–73)
Clinical stage of primary tumor (AJCC)	
IB	8 (23.5)
II	9 (26.5)
III	17 (50.0)
Indications	
Recurrence in stump	13 (38.2)
Stump infiltration after nonradical surgery	21 (71.8)
Histopathology	
Squamous cell carcinoma	25 (73.5)
Others	9 (26.5)
Treatment	
Brachytherapy only 4 × 7.5 Gy	25 (73.5)
Brachytherapy 2 × 6 Gy + EBRT 50 Gy	9 (26.5)
Zubrod (WHO)[a]	
0	12 (35.3)
1	22 (64.7)
Dyspnea[a]	
0 + 1	11 (32.4)
2 + 3	23 (67.6)
Cough[a]	
1	21 (61.8)
2	13 (38.2)
Hemaptosis[a]	
0	26 (76.5)
1 + 2	8 (23.5)

AJCC = American Joint Committee of Cancer; WHO = World Health Organization; EBRT = external beam radiation therapy.

[a] Before treatment, according to Speiser and Spratling scale, published in (14).

Treatment

Brachytherapy was performed under local anesthesia and sedation with midazolam. One bronchial Lumencath French 6 applicator (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) was placed in the bronchus stump during bronchofiberoscopy and under endoscopic control (Fig. 1a and 1b). We checked the catheter position after bronchoscopy with x-ray in the same position in which the patient was irradiated. The target volume was defined by the prior CT scans made every 3 mm. To calculate the dose distribution, the Oncentra 3.0 planning system (Nucletron, an Elekta company) was employed. The distance between the prescription point and the catheter was defined according to the target diameter (median range, 0.5–1 cm). It means that the target volume included the stump with a 1- to 2-cm margin on CT. A high-dose-rate afterloading unit—Microselectron HDR (Nucletron, an Elekta company)—with an ^{192}Ir stepping source and a nominal activity of 370 GBq (10 Ci) was used. The brachytherapy schema consisted of a sole brachytherapy group given 4 fractions of 7.5 Gy given weekly, and a second group given 2 fractions of 6 Gy. In 9 cases, EBRT was used (fraction dose, 2 Gy; total dose, 50 Gy) after brachytherapy owing to organizational reasons (immediate possibility to start brachytherapy).

Methods

Patients were under clinical and endobronchial observation with regard to survival and local remission rates, and subsiding dyspnea, breathing, cough, and hemoptysis. Symptoms were evaluated according to Speiser and Spratling scale, published in (14). Overall survival time (OS) and overall disease-free survival time (OFS) were compared with

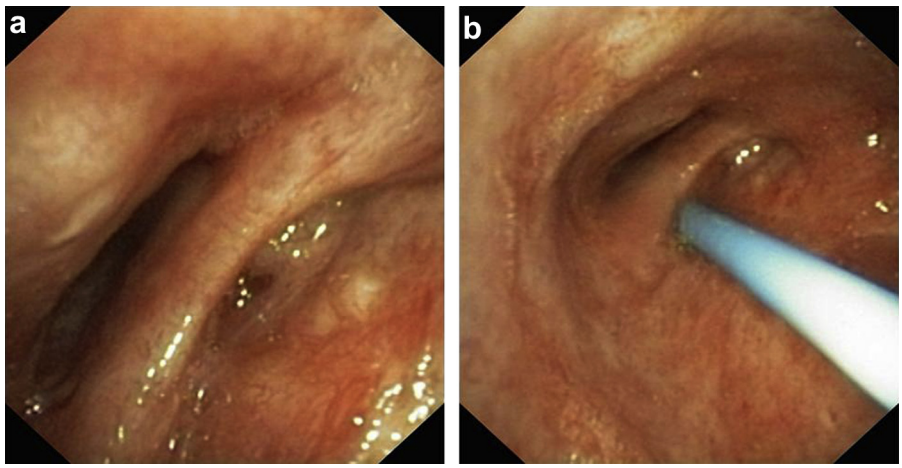

Fig. 1. (a) Bronchial stump visible during bronchofiberoscopy. (b) Lumencath French 6 applicator (Nucletron, an Elekta company) fixed in stump.

chosen clinical data: Age, gender, histopathology, clinical stage of primary tumor, Eastern Cooperative Oncology Group-Zubrod-World Health Organization score, remission of tumor assessed after 1 month and protocol of treatment. Grade of remission was assessed after the first month using bronchofiberoscopy and CT scans. The results were divided into four categories: (*1*) Complete remission—symptoms subsiding and total regression observed during bronchofiberoscopy, (*2*) partial remission, (*3*) no remission, or (*4*) progression. Partial remission was defined as 50% reduction of tumor volume estimated during bronchofiberoscopy. Complete remission and progressive disease were defined as no evidence of local tumor or further tumor growth of >25% (2).

Statistical evaluation

The material was analyzed on the basis of retrospective observation of the course of the disease. Survival time was defined as time from the beginning of brachytherapy to the death of the patient or to the end of observation. For univariate categorized data analysis, the log-rank test and Peto and Peto Wilcoxon test were used. For data showing statistical significance in univariate analysis, a multivariate analysis (Kaplan–Meier) model was used; $p < 0.05$ was considered significant.

Results

The median followup was 2 years (range, 3 months to 4 years). The complete local and radiologic response rate, evaluated in the first month after HDR-BT, was 73.5% (25/34) with 100% complete remission in the second group (nonradical surgery); the partial response rate was 26.5% (9/34), but partial remission was observed in 9 of 13 recurrent tumors (69.2%). Median OFS was 17.4 months, and OS was 18.8 months for the total group (Fig. 2). OS/OFS

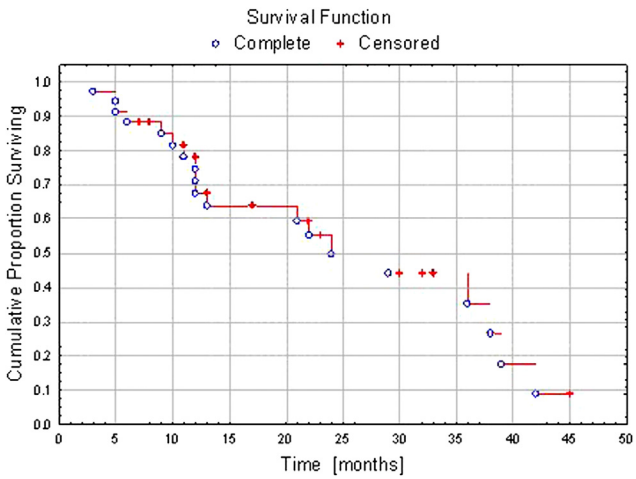

Fig. 2. Overall disease-free survival time (OFS) in the whole group of patients.

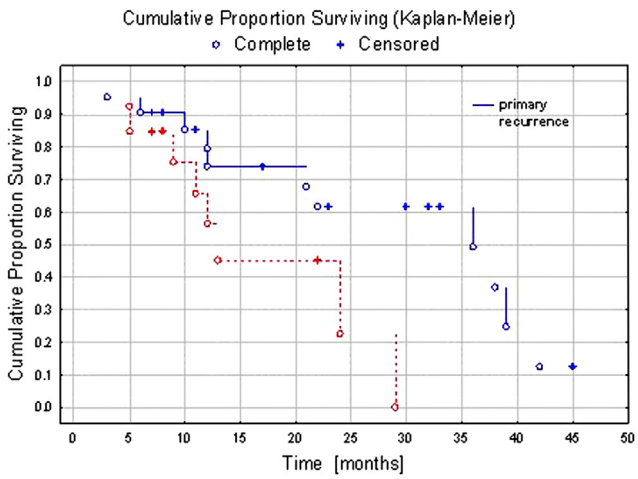

Fig. 3. Overall disease-free survival time (OFS) depending on reason for high-dose-rate brachytherapy (HDR-BT) of a stump: Local recurrence in stump or adjuvant therapy after nonradical surgery (Cox's F-test, $p = 0.19924$; Peto and Peto Wilcoxon test, $p = 0.04714$; log-rank test, $p = 0.04784$).

Table 2
Brachytherapy treatment schema (indications, doses) (21, 23)

Indications for brachytherapy	Phase I	Phase II	Phase III	Phase IV
Radical combined treatment: schema I, clinical stage T1−3 N1−3 M0	EBRT: total dose 44 Gy in 22 fr. aa 2 Gy (2 a-p fields)	1 fr. ×6 Gy, ref. point 0.5−1 cm	EBRT 16 Gy in 8 fr. (changed fields)	1 fr. ×6 Gy, ref. point 0.5−1 cm
Radical combined treatment: schema II, clinical stage T1−3 N1−3 M0	EBRT: total dose 44 Gy in 22 fr. aa 2 Gy (2 a-p fields)	EBRT 16 Gy in 8 fr. (changed fields)	HDR-BT in 1, 3, and 5 weeks of EBRT, 3 × 10 Gy	—
Radical sole treatment, radiologically occult cancer T1−2N0	Total dose 36−42 Gy in 6−7 fr. with interval of 4−7 days between fractions	—	—	—
Radical treatment after surgery, R2	After EBRT with total dose of 50−60 Gy	To consider increasing the total use using HDR-BT HDR. Fr. dose from 1 × 6 Gy until 3 fr. ×6 Gy (18 Gy), depending on EBRT dose	—	—
Radical treatment: stump infiltration	Brachytherapy only: 4 fr. of 7.5−10 Gy with interval of 4−7 days between fractions	—	—	—
Palliative treatment	Total dose 18 Gy in 3 fr. of 6 Gy with interval of 4−7 days in patients treated earlier with EBRT, dose >50 Gy	—	—	—
	Total dose 22.5 Gy in 3 fr. of 7.5 Gy Gy with interval of 4−7 days in patients not irradiated or treated earlier with EBRT, dose <50 Gy	—	—	—
	1 × 10 Gy in case of WHO scale >2	Sometimes dose can be repeated after few weeks, in cases with clinical remission or visible during bronchoscopy	—	—

Fr. = fraction; EBRT = external beam radiation therapy; HDR-BT = high-dose-rate brachytherapy; WHO = World Health Organization.

was significantly associated with treatment qualification: Recurrence (first group) or nonradical surgery (second group; log-rank test, $p = 0.048$; Fig. 3). In the first group (recurrence), the 1-year OS rate was 53.9% (7 of 13), the OFS rate was 30.8% (4 of 13), the 2-year OS rate was 15.4% (2 of 13), and the OFS rate was 7.7% (1 of 13). In the second group (nonradical surgery), the 1-year OS and OFS rate was 71.4% (15 of 21), 2-year OS rate was 47.6% (10 of 21), and the OFS rate was 42.9% (9 of 21). No differences were noted according to age ($p = 0.69$), gender ($p = 0.36$), clinical stage ($p = 0.76$), histopathology ($p = 0.93$), treatment doses ($p = 0.45$), sole or combined treatment ($p = 0.16$), or grade of remission in the fourth week after HDR-BT ($p = 0.15$; Fig. 3). We analyzed also correlations between OS and features describing the general condition of the patient and the symptoms before treatment. Significant correlations were not found between OS/OFS and Eastern Cooperative Oncology Group-Zubrod-World Health Organization score ($p = 0.37$), dyspnea ($p = 0.95$), cough ($p = 0.97$), hemoptysis ($p = 0.67$), or pain in chest ($p = 0.22$).

Discussion

Indications for definitive brachytherapy widely published (2, 14–22) include (*1*) brachytherapy in combined treatment as a boost after EBRT, in clinical stage T1-2N0-1M0 in patients who do not qualify for surgery, with or without chemotherapy, dose increase using HDR-BT (''boost'') should decrease local recurrence rate; (*2*) as sole brachytherapy, in clinical stage T1-2N0M0, in patients with occult carcinoma or tumors potentially resectable, with a diameter of <2 cm, disqualified for surgery or EBRT; (*3*) supplementary treatment (with or without EBRT) after surgery R2; brachytherapy could play an important role in cases with positive margins after resection (stump histopathology). Commonly used treatment schemata are listed in Table 2.

Endobronchial HDR-BT as the sole method of treatment is a viable alternative in a selected group of patients with small, well-localized primary or recurrent lung cancers, not amenable to treatment by traditional methods. The prescription point should be adjusted based on the actual depth of the tumor volume as delineated on CT, and placement of the catheter and its relation to the normal bronchial mucosa and adjacent vascular structures. The optimal technique implies a central endoluminal placement of the catheter, avoiding direct contact with the normal mucosa. This is not always possible. The results obtained are satisfactory and much superior to any of the other alternatives for endoluminal therapy without any significant added morbidity (3). Definitive brachytherapy was frequently performed in clinical research, published results come primarily from U.S. and Japanese clinics. Analysis of the results shows that only small group of patients in early T1N0 stage can be a target for this kind of treatment. Chosen published papers are presented in Table 3. Analyzing presented results we find that median followup was 2–3 years; survival rate and local control rate were high probably owing to selected group of patients with early T1N0 clinical stage.

Combined radical treatment with EBRT

Combined radical treatment was also a subject of many publications, but patients groups were relatively small. Table 4 presents some published observations. Published results suggest that, with the combination of EBRT and HDR-BT, postobstructive features such as pneumonitis and atelectasis are likely to be treated more adequately compared with EBRT alone. This could also account for the higher response rates for those respiratory symptoms associated with postobstructive features, in particular for dyspnea (33, 34). In some cases, dyspnea is a result of endobronchial obturation and a presence of tumor mass (2, 18, 33, 35). Even papers published years ago are valuable. Speiser and Spratling (14) reported on a prospective study among 342 patients with endobronchial tumors treated by the combination of EBRT (30–60 Gy) and concomitant HDR-BT during weeks 1, 3, and 5. The results achieved with this approach were remarkable, with response rates of 99% for hemoptysis, 85% for cough, and 86% for dyspnea. In a retrospective study, Chang *et al*. (29) reported comparable results with the combination of EBRT (20–70 Gy) and concomitant BT (3 × 7 Gy HDR) during weeks 2, 4, and 6. They observed response rates of 79% for cough, 95% for hemoptysis, and 87% for dyspnea. Results published by Langendijk *et al*. (34) suggest that the addition of HDR-BT to EBRT in non–small-cell lung cancer is safe and provides greater rates of reexpansion of collapsed lung, resulting in a transient

Table 3
Curative brachytherapy as monotherapy for radiographically occult endobronchial carcinoma: Treatment results

Author	*n*	Clinical stage	Brachytherapy schema (fractions, Gy)	Reference point (mm)	OFS (%)	CR (%)	LR (%)
Tredaniel *et al*. (7)	14	Limited to wall	3 × 7	10	NA	84	14
Ardiet *et al*. (9)	28	<10 mm–CT (–)	3–5 × 7	10	NA	84	24
Perol *et al*. (11)	19	<10 mm–CT (–)	3–5 × 7	10	58 at 2 y	83	5
Taulelle *et al*. (12)	22	Limited to wall	3–5 × 7–10	10	46 at 3 y	96	18
Hennequin *et al*. (10)	73	<20 mm–CT (+)	5–6 × 7	5–15	45 at 2 y	—	41
Marsiglia *et al*. (3)	34	2–40 mm	6 × 5	5–10	78 at 2 y	85 at 2 y	15

OFS = overall free survival (years of followup); CR = complete remission; LR = local recurrence; CT = computed tomography; NA = no data.

Table 4
Curative brachytherapy combined with EBRT: (*1*) Radiographically occult endobronchial carcinoma (*2*) in IIIA and IIIB lung cancers, summarized results

Author	*n*	Clinical stage	EBRT (Gy)	Brachytherapy schema (Gy)	LC (%)	OFS (%)
EBRT + LDR (radiographically occult endobronchial carcinoma)						
Fuwa *et al.* (13)	17	Chest x-ray negative	50 (30–77)	22 (10–42)	100	90
Saito *et al.* (5)	68	Chest x-ray negative	40	25	87	—
EBRT + MDR						
Fuwa *et al.* (23)	39	—	45 (22–66)	28 (10–46)	97	87
EBRT + HDR						
Mantz *et al.* (24)	39	T1, 2 ≤ 5 cm	54–75.6	(*1*) 2–4 fr. × 5–7 Gy; (*2*) no BT	5 y: EBRT + BT, 58%; EBRT, 32%	NS
Huber *et al.* (25)	68	Advanced central lung tumors	60	Trial: (*1*) 2 fr. × 4.8 Gy; (*2*) no BT	5 vs. 3 mos ($p = 0.052$)	10 vs. 8 mos ($p = 0.09$)
Reddi *et al.* (26)	32	IIIA–IIIB	60	3 fr. ×7.5 Gy	—	8 mos
Aygun *et al.* (27)	62	IIIA–IIIB	50–60	3–5 fr. ×5 Gy	—	13 mos
Mehta *et al.* (28)	22	IIIA–IIIB	60	4 fr. ×4 Gy	—	8.5 mos
Chang *et al.* (29)	54	IIIA–IIIB	20–70	3 fr. ×7 Gy	—	—
Cotter *et al.* (30)	65	IIIA–IIIB	55–66	2–4 fr. ×2.7–10 Gy	86	8 mos
Speiser and Spratling (14)	50	IIIA–IIIB	60	3 fr. ×7.5–10 Gy	80	11 mos
Kohek *et al.* (31)	39	III	50–70	1–5 fr. ×5.6 Gy	67	13 mos
Zajac *et al.* (32)	24	III	50–61.2	3 fr. ×5–10 Gy	82	12 mos

LC = local control; OFS = overall free survival; BT = brachytherapy; LDR = low-dose rate; MDR = medium-dose rate; HDR = high-dose rate; EBRT = external beam radiation therapy; y = years; mos = months; fr. = fractions; Gy = Gray.

lower level of dyspnea. This beneficial effect was observed only among patients with obstructing tumors in the main bronchus. Similar results were published by Harms *et al.* (36). Mantz *et al.* (24) divided 39 patients with early bronchial cancer into two groups, one treated with EBRT and a second treated with EBRT and HDR-BT. The local control rate was significantly greater in the second group (5 years followup; 58% vs. 32%). They observed no difference in OS. However, the definitions used for response of symptoms, reexpansion of collapsed lung, and the methods used to assess these responses differed greatly among these studies. Moreover, the inclusion criteria of these studies differed widely and no randomized studies have been published investigating the additional value on palliation of respiratory symptoms of HDR-BT plus EBRT versus EBRT alone. Therefore, the additional value of HDR-BT concomitantly with EBRT is not yet well-defined (34).

In one of published papers, the role of brachytherapy in irradiation of recurrence in stump is mentioned (37). Zimmermann *et al.* noted that approximately 1–2% of all recurrent lung cancers are treated with curative reoperation, with somewhat dismal results. EBRT has been used for either postoperative or post-RT locoregional recurrences. In the former case, external beam RT was particularly effective in isolated bronchial stump recurrences, with a median survival time of approximately 28.5 months and a 5-year survival of approximately 31.5%. In the latter case, re-irradiation, generally with endobronchial brachytherapy, was successful in palliation of intrathoracic symptoms (in at least two-thirds of cases), carrying a low incidence of radiation pneumonitis (up to 5%) although cumulative doses went up to 120–150 Gy. In addition to external beam RT, endobronchial RT was used to treat symptomatic intraluminal recurrences, with the vast majority of studies using HDR-BT (37).

HDR-BT as a curative, definitive treatment has not been extensively studied, especially in stump recurrences or after nonradical surgery (lobar resection) with the presence of cancer cells in surgical margin. We believe that in limited disease (small target size, target volume) brachytherapy can achieve satisfactory results. We noted an OFS of 17.4 months and OS of 18.8 months. Important differences in OS/OFS were observed owing to qualification for HDR-BT. Patients with recurrence in a stump had worse prognosis, probably because they had more advanced disease at time of primary treatment or more aggressive tumors. Relatively small numbers of patients could be the reason why we found no correlations between OS, OFS, and analyzed clinical factors.

Conclusions

HDR-BT of a stump recurrence or after nonradical resection achieves a long-term, cause-specific survival rate of the patients with localized lung cancer and could be considered curative. Brachytherapy treatment is cost sparing: The time of hospitalization of the patient during EBRT is longer (in Poland a standard), brachytherapy can be carried out on outpatients basis, resulting in greater comfort for the patient. We can treat a greater number of patients daily (fewer treatment fractions); we have a shorter waiting time for the start of treatment. Treatment results are

promising in selected groups of patients eligible for radical treatment, but the number of patients qualified for such treatment remains low.

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